Review Article

# Post-caesarean analgesia: What is new?

**Address for correspondence:**
Dr. Sukhyanti Kerai,
B 3/59, Upper Ground Floor,
Paschim Vihar,
New Delhi, India.
E-mail: drsukhi25@gmail.com

*Sukhyanti Kerai, Kirti Nath Saxena[1], Bharti Taneja[1]*
Department of Anaesthesiology, Rajiv Gandhi Super Speciality Hospital, [1]Department of Anaesthesiology and Intensive Care, Maulana Azad Medical College and Associated Hospitals, New Delhi, India

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## ABSTRACT

Adequate post-operative analgesia after caesarean section (CS) is vital as it impacts the distinct surgical recovery requirements of the parturient. Although newer analgesic modalities and drugs for post-caesarean analgesia have been introduced over the recent years, review of the literature suggests suggests that we are far from achieving the goals of optimum post-operative analgesia. We conducted a systematic review of recent advances in modalities for post-caesarean analgesia. After systematic search and quality assessment of studies, we included a total of 51 randomised controlled trials that evaluated the role of opioids, transversus abdominis plane (TAP) block, wound infiltration/infusion, ketamine, gabapentin and ilioinguinal-iliohypogastric nerve block (II-IH NB) for post-caesarean analgesia. Administration of opioids still remains the gold standard for post-operative analgesia, but the associated troublesome side effects have led to the mandatory incorporation of non-opioid analgesics in post-CS analgesia regime. Among the non-opioid techniques, TAP block is the most investigated modality of the last decade. The analgesic efficacy of TAP block as a part of multimodal analgesia is established in post-CS cases where intrathecal morphine is not employed and in CS under general anaesthesia. Among non-steroidal anti-inflammatory drugs, COX-I inhibitors and intravenous paracetamol are found to be useful in post-operative analgesic regimen. The perioperative use of ketamine is found useful only in CS done under spinal anaesthesia; no benefit is seen where general anaesthesia is employed. Wound infiltration with local anaesthetics, systemic gabapentin and II-IH NB need further trials to assess their efficacy.

**Key words:** Anaesthesia, caesarean section, post-caesarean analgesia

## INTRODUCTION

Pain is ranked highest among undesirable clinical outcomes associated with caesarean section (CS).[1] Adequate post-operative analgesia in the obstetric patients is crucial as they have different surgical recovery needs which include breastfeeding and care of the newborn; these can be impaired if analgesia is unsatisfactory. The ideal post-CS analgesic regime should be efficacious without impacting the ability of mother to take care of the neonate and with minimal drug transfer through breast milk. However, observational data from developing as well as developed countries have shown that we are far from achieving these goals. In developing countries, limited availability of drugs, equipment and expertise are the major issues in providing adequate post-CS analgesia.[2] In the past 5 years, there has been a surge in studies describing newer post-operative analgesic modalities. Some of these modalities require less expertise and reduce consumption of opioids in post-operative period.

## LITERATURE SEARCH

This systematic review examined the recent advances in modalities for post-operative analgesia after CS. We searched US National Library of Medicine database, Cochrane Central Register of Controlled Trials, EMBASE and CINAHL for randomised controlled trials (RCTs) that evaluated various analgesic modalities after CS. The terms post-operative analgesia, CS, post-caesarean



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analgesia were searched. The search was performed without any limits or language restrictions. The last search was performed on 15 October 2016. It revealed a total of 738 results. The RCTs published before 2010, review articles, retrospective studies, case reports and letter to the editor were excluded. After this, a total of 102 RCTs on various types of analgesic were available [Figure 1].

## RESULTS

The various analgesic modalities identified were transversus abdominis plane (TAP) block, local anaesthetic wound infiltration, non-steroidal anti-inflammatory drugs (NSAIDs) and acetaminophen, ilioinguinal-iliohypogastric nerve blocks (II-IH NBs), intrathecal additives, epidural analgesia, ketamine and gabapentin. The quality of the selected RCTs was assessed by two independent reviewers using the Jadad scale. Based on consensus of all authors, the studies scoring >3 on the Jadad scale were selected for data collection and further review.

A standardised data collection form was used for outcome data extraction. Data recorded were trial characteristics including sample number, anaesthesia technique, post-operative regimen employed and outcome measures such as post-operative opioid consumption, pain scores and side effects. Based on this data, we describe the utility of intrathecal and epidural opioids, TAP block, II-IH NB and wound infiltration, ketamine, NSAIDs, acetaminophen and gabapentin for post-CS analgesia.

## INTRATHECAL AND EPIDURAL OPIOIDS

In the present review, we found 13 RCTs on various intrathecal opioids used for post-caesarean analgesia; eight trials were excluded after evaluating them. The remaining five RCTs [Table 1] were taken up for review; out of these two trials evaluated the different doses of intrathecal morphine (ITM) while three studied lipophilic opioids fentanyl and sufentanil.

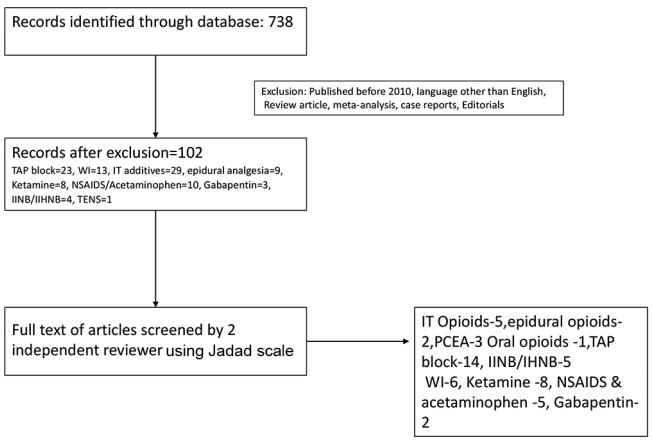


**Figure 1:** Flow diagram of review

The efficacy of ITM for post-CS pain control is well established, but the optimal dose is still debated. Previous investigators reported 100 μg ITM to be equivalent to higher doses both in terms of analgesia and side effects.[3] A further lower dose of 50 μg with 100 μg ITM was evaluated in two studies and found to be equally efficacious.[4,5] These results showed that there is no direct relationship between the dose of ITM and the quality of analgesia. Similar results were demonstrated in previous studies by other investigators.[3,6] The incidence of pruritus after ITM was found to increase linearly with increasing dose while other side effects such as urinary retention, nausea and vomiting were found to bear no relation with either the use or the dose of ITM. Neither of the two studies reported respiratory depression or sedation which may be attributed to the small sample size of the studies.

Lipophilic opioids such as fentanyl and sufentanil given intrathecally, when compared to ITM, were found to provide only early post-operative analgesia.[7] The comparison of intrathecal fentanyl and sufentanil showed that sufentanil provides longer post-operative analgesia without increased incidence of side effects.[8,9]

We found one RCT each on epidural morphine and lipophilic opioids [Table 1]. Traditionally, the dose of epidural morphine used for post-CS analgesia is 2–3 mg.[10] Recently an RCT on epidural morphine compared traditional dose of 3 mg to a lower dose of 1.5 mg. The authors found the 1.5 mg of epidural morphine to be equally efficacious and associated with lower incidence of nausea and pruritus.[11]

Vora *et al*. studied a combination of epidural lipophilic opioid with a small amount of hydrophilic opioid and observed the additional benefit of immediate onset as compared to morphine alone.[12]

## PATIENT CONTROLLED EPIDURAL ANALGESIA

Patient-controlled epidural analgesia (PCEA) has shown effective post-CS analgesia in three studies

**Table 1: Opioids administered through various routes for post-caesarean analgesia**

| Studies | Dose and route of opioids | Results | Conclusions |
|---|---|---|---|
| Intrathecal opioids | | | |
| Mikuni *et al*. (2010) | 76 patients undergoing caesarean section under combined spinal-epidural anaesthesia were randomised into three groups<br>Group 0: No ITM; only 8 mg of hyperbaric bupivacaine<br>Group 50: 50 µg of ITM<br>Group 100: 100 µg of ITM<br>Each patient received epidural 0.2% ropivacaine infusion for post-operative analgesia | Groups receiving ITM had lower pain scores and less rescue analgesic requirement than Group 0<br>Higher incidence of pruritus in group 100 but not Group 50 when compared to group 0 | 50 µg and 100 µg of intrathecal morphine improve analgesia when combined with a continuous epidural infusion of ropivacaine after CS<br>50 µg of intrathecal morphine is associated with a low frequency of side effects |
| Carvahlo *et al*. (2013) | 123 patients were randomised into two groups<br>Group 50: 50 µg of ITM<br>Group 100: 100 µg of ITM added to 12 mg of 0.5% hyperbaric bupivacaine | No significant difference in pain intensity and analgesic consumption in both groups<br>Statistically significant higher incidence of pruritus in group receiving 100 µg ITM | Intrathecal morphine 50 µg provides the same quality of analgesia as 100 µg, with a lower incidence of side effects |
| Swai *et al*. (2013) | 60 patients randomised into two groups<br>Group I: 1.8-2 ml of 0.5% hyperbaric bupivacaine + 25 µg ITF+0.1 mg ITM<br>Group II: Only ITF with bupivacaine; no ITM | Group receiving ITM with ITF had significantly lower pain scores up to 20 h postoperatively<br>Incidence of pruritus, nausea and vomiting were statistically significant up to 12 h post-operative in ITM group | Addition of ITM along with intrathecal bupivacaine and fentanyl resulted in better post-operative analgesia compared to ITF with bupivacaine alone |
| Oziyakan *et al*. (2013) | 93 patients were randomised into three groups<br>Group C: 0.5% levobupivacaine (2.2±0.2 mL)<br>Group S: 2.5 µg sufentanil plus 0.5% levobupivacaine (2.2±0.2 mL)<br>Group F: 10 µg fentanyl plus 0.5% levobupivacaine (2.2±0.2 mL) intrathecally | Time of first analgesic requirement was longer ($P$<0.001) in Group S compared to Group F or Group C<br>Additional analgesic requirement during the first 24-h period was lowest in Group S, and highest in Group C ($P$<0.001)<br>Post-operative pruritus was more frequent in Group S ($P$<0.001) | Addition of sufentanil and fentanyl to intrathecal levobupivacaine during caesarean section surgery extended the duration of post-operative analgesia and led to a decrease in total analgesic requirement |
| Wilwerth *et al*. (2016) | 180 full-term parturients undergoing elective caesarean section were randomly allocated into 3 groups, according to the opioid added to 10 mg intrathecal hyperbaric bupivacaine: fentanyl 25 µg, sufentanil 2.5 µg or sufentanil 5 µg | Duration of post-CS analgesia was significantly longer in sufentanil 2.5 µg and 5 µg compared to 25 µg of ITF<br>Morphine consumption was lower in sufentanil groups compared to fentanyl groups ($P$<0.001) | Intrathecal sufentanil 5 µg is the opioid of choice compared to 2.5 µg sufentanil and 25 µg fentanyl, associated with the best quality of anaesthesia without increased incidence of side effects |
| Epidural opioids | | | |
| Singh *et al*. (2013) | 90 parturients are randomly allocated to receive either 3 mg or 1.5 mg EM | Median 24 h opioid consumption between 1.5 mg EM and 3 mg EM was 0 mg (one-sided 95%, 2.5 mg)<br>This CI was below the pre-specified non-inferiority margin of 3.33 mg | There were no significant differences observed between groups in the median 24-48 h opioid consumption |
| Vora *et al*. (2011) | 60 patients are randomly allocated to sufentanil 50 mcg in Group S; morphine 4 mg in Group M; and, a combination of sufentanil 25 mcg and morphine 2 mg was used in Group SM | Onset of action were at 7.6±1.5 min in Group S, 67.6±1.5 min in Group M and 12.2±2.6 min in Group SM<br>Duration of analgesia was longer in Group M 17.5±1.9 h and SM 13.8±1.6 h than in Group S 5.2±1.2 h | Combination of sufentanil and morphine administered epidurally, for post-caesarean section analgesia, offers the advantage of a more rapid onset as well as longer duration of analgesia, with fewer side effects, than the two drugs used alone |

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**Table 1: Contd...**

| Studies | Dose and route of opioids | Results | Conclusions |
|---|---|---|---|
| PCEA | | | |
| Matsota *et al*. (2011) | 60 pregnant women undergoing elective CS were randomised to three groups<br>Ropivacaine 0.15% plus fentanyl 2 μg/ml (basal rate 6 ml/h, bolus 4 ml/20 min)<br>Ropivacaine 0.15% (basal rate 5 ml/h, bolus 4 ml/20 min)<br>Levobupivacaine 0.15% (basal rate 5 ml/h, bolus 4 ml/20 min) | No significant difference in total local analgesic consumption, rescue analgesic requirements and pain scores between the groups<br>A significantly higher sympathetic and sensory blockade occurred with levobupivacaine and ropivacaine 0.15% compared to ropivacaine 0.15% plus fentanyl<br>Higher patient satisfaction in ropivacaine 0.15% plus fentanyl compared to other two groups | PCEA with dilute local anaesthetic solutions of levobupivacaine 0.15%, ropivacaine 0.15% and ropivacaine 0.15% plus fentanyl 2 μg/ml provides satisfactory post-operative analgesia after CS |
| Cohen *et al*. (2015) | 48 parturients undergoing elective CS under lumbar epidural anaesthesia were randomised into four groups receiving different concentrations of ropivacaine with fentanyl 3.0 μg/ml and epinephrine 0.5 μg/ml for PCEA<br>Group I: Ropivacaine 0.2%<br>Group II: Ropivacaine 0.1%<br>Group III: Ropivacaine 0.05%<br>Group IV: Ropivacaine 0.025% | Pain scores at rest were lower for Group IV than Groups I-III ($P$<0.001)<br>12, 5, 1 and 0 patients could not ambulate in Groups I-IV, respectively<br>9, 9, 2 and 0 (III <I and II, $P$=0.02; IV <I and II, $P$=0.001) patients reported urinary retention in Groups I-IV, respectively<br>Overall satisfaction scores were high for all groups | 0.025% ropivacaine PCEA combined with fentanyl and epinephrine provided effective pain relief after CS |
| Chen *et al*. (2014) | 80 patients were randomly assigned to two groups<br>Group A: 40 patients received epidural drug solution made of 0.6 mg/ml levobupivacaine plus 2 mcg/ml fentanyl<br>Group B: 1 mg/ml of levobupivacaine alone<br>PCEA settings: 2 mL for bolus, 3 mL/h for continuous infusion, a 20-minutelockout interval and a 4-h limit of 30 mL | No difference between groups in VAS scores and the total volume of drugs consumed<br>Higher incidence of dizziness and pruritus in Group A | PCEA levobupivacaine with fentanyl has more dizziness and pruritus and less paraesthesia than PCEA levobupivacaine alone<br>Pure levobupivacaine could be an alternative regimen for parturients who have had previous negative experiences with or are concerned about opioid-related adverse events |
| Oral opioids | | | |
| McDonnell *et al*. (2011) | 120 parturients were allocated to two groups<br>Group O: Sustained-release oral oxycodone 20 mg in the recovery room followed by immediate-release oxycodone 10 mg 6-hourly for the first 24 h<br>Group I: Intrathecal morphine 100 μg at the time of spinal anaesthesia | Time to first analgesic request was similar, but additional post-operative analgesics were required more often in Group O (82% vs. 63%) $P$=0.034<br>Numerical pain scores were low and similar, except at rest at 12 h ($P$=0.030)<br>Group O more frequently reported high worst pain scores ($P$=0.007)<br>Pruritus was more common and more severe in Group I ($P$ =0.001)<br>At 24 h maternal satisfaction with the analgesic regimen was lower in Group O ($P$=0.010) | Oral oxycodone produced comparable post-operative pain relief to intrathecal morphine with a lower incidence of pruritus but was associated with a lower satisfaction score |

ITM – Intrathecal morphine; PCEA – Patient-controlled epidural analgesia; ITF – Intrathecal fentanyl; EM – epidural morphine; CS – Caesarean section; CI – Confidence interval; VAS – Visual analogue scale

using opioids with local anaesthetic (LA) agents [Table 1]. Satisfactory post-operative analgesia has been reported with dilute concentrations of ropivacaine 0.025%–0.15% and 0.15% levobupivacaine.[13] Combining a lipophilic opioid like fentanyl or sufentanil to ropivacaine has an LA sparing effect with lower incidence of motor blockade in parturients.[14] However, with the addition of fentanyl to levobupivacaine, greater dizziness and pruritus and less paraesthesia is reported than with PCEA levobupivacaine alone.[15] Pure levobupivacaine could be an alternative regimen for the parturient who is concerned about opioid-related adverse events.

## CURRENT STATUS OF ORAL OPIOIDS

Traditionally, oral opioids are employed as a step down analgesics for post-operative analgesia when the severity of pain decreases. Recently, there has been growing interest in their use as the primary post-caesarean analgesic method on the first post-operative day itself. The potential benefits of this approach include higher maternal acceptability, ease of administration and avoidance of complications associated with parenteral or neuraxial opioids. Oral oxycodone is the preferred opioid for such an approach, as it has a higher and more predictable oral bioavailability than morphine.[16] Oral oxycodone-based post-operative oral regime has been found equianalgesic to ITM after CS.[17]

For oral methadone and tramadol; we could not find any study scoring >3 on Jaded scale in the present review.

## REGIONAL NERVE INFILTRATION TECHNIQUE: TRANSVERSUS ABDOMINIS PLANE BLOCK

A total of 14 studies [Table 2] employing TAP block for post-CS analgesia were identified.[18-31] Most of the investigators used ultrasound-guided TAP block; only in two studies TAP block was performed by anatomical landmark technique.[20,21]

There are three studies where TAP block was compared to control for post-CS analgesia and all three demonstrated block to be effective.[18,21,22] In two of these studies, CS was performed under general anaesthesia while in the third study spinal anaesthesia was administered. However, when compared to ITM, TAP block was reported to be ineffectual in three studies.[19,20,23] There was also no advantage of supplementing ITM with TAP block as concluded in two trials.[29,31] The researchers also studied various other approaches to increase the efficacy of TAP block in comparison to ITM. These included adding clonidine or fentanyl and increasing the dose of LA, but all of them failed to show any benefit.[24,27,30] When TAP block was compared as a part of multimodal analgesia comprising epidural morphine, less consumption of patient-controlled analgesia (PCA) morphine was noted.[28] In two other studies, TAP block was observed to be equally effective in comparison to wound infiltration for analgesia.[25,26]

TAP block as a part of multimodal analgesia after CS is useful in reducing opioid consumption and their side effects only in parturient receiving general anaesthesia or in situations where ITM is not used. The probable explanation for this may be that since ITM already provides effective analgesia for somatic and visceral afferents, post-operative analgesia is not improved by adding TAP block to ITM. Further, larger studies with adequate power and evaluation of lower dose of ITM with TAP block need to be evaluated.

## ILIOINGUINAL-ILIOHYPOGASTRIC NERVE BLOCK

There are five studies on II-IH NB for post-CS analgesia [Table 3].[32-36] In three studies,[32-34] the block was performed by the blind bilateral multilevel II-IH NB technique described by Bell *et al*.[37] In one trial[35] a single injection as described by Huffnagle *et al*.[38] was used and, in another, an ultrasound-guided block[36] was performed. In all these trials, except the one using ultrasound for nerve blockade, II-IH NB was seen to be effective for post-CS analgesia. The authors attribute the negative result to use of ITM for spinal anaesthesia which they considered 'standard of care'. However, Wolfson *et al*. found the landmark-based II-IH NB in addition to ITM to be effective in enhancing analgesia after CS.[34] The ultrasound-guided block is of moderate level difficulty and needs accurate visualisation of nerves. The drug is placed by out of plane approach till the nerves are seen to be completely surrounded by the drug. Further studies involving ultrasound-guided II-IH NBs are warranted to establish its analgesic efficacy.

## WOUND INFILTRATION/CONTINUOUS WOUND INFUSION WITH LOCAL ANAESTHETICS

There are two studies[39,40] of single shot wound infiltration and four RCTs of continuous wound infusion[41-44] for post-caesarean analgesia [Table 4]. The drug used for infusion/infiltration is LA in six while in one study tramadol infiltration was compared to LA.[40]

The trials comparing LA for continuous wound infusion have conflicting results. Most trials found continuous wound infusion to be less effective as compared to placebo[41] or ITM[42] or epidural levobupivacaine[40] whereas one found it to be equally effective to epidural morphine in post-operative analgesic requirement.[43] Rackleboom *et al*. demonstrated that placement of catheter for continuous wound infusion between transversalis fascia and peritoneum

**Table 2: Studies using transversus abdominis plane block for post-caesarean analgesia**

| Study | Anaesthesia technique | TAP block technique | Post-operative analgesic regime | Outcomes |
|---|---|---|---|---|
| Baaj *et al*. (2010) | Spinal anaesthesia with 20 µg ITF | US-guided TAP block versus control<br>20 ml of 0.25% bupivacaine per side | Morphine PCA | TAP block resulted in reduction of morphine consumption to more than 60%, improved satisfaction with their pain relief over 24 h after surgery, less nausea, vomiting and better patient's satisfaction |
| Kanzai *et al*. (2010) | SAB with hyperbaric bupivacaine and saline in TAP group<br>SAB with hyperbaric bupivacaine and 100 µg ITM in SAM group | US-guided TAP block<br>20 ml of 0.375% bupivacaine with epinephrine (5 µg/ml) per side | Acetaminophen 1 g/6 h (intravenously on 1st day and oral on 2nd day) + rectal diclofenac 100 mg/12 h + IV tramadol 100 mg/8 h on patients request | SAM group has longer time to the first analgesic requirement, less number of tramadol doses received and lower pain scores<br>Higher incidence of pruritus and nausea in SAM group |
| McMorrow *et al*. (2011) | Spinal anaesthesia with 10 µg ITF<br>100 µg of morphine in ITM groups in addition to hyperbaric bupivacaine and 10 µg ITF | TAP block using landmark technique versus control ($T_{LA}$ vs. $S_S$)<br>TAP block using landmark technique versus control (both group receiving ITM with spinal anaesthesia) ($T_S$ vs. $S_M$)<br>TAP block using landmark technique versus ITM ($T_{LA}$ vs. $S_M$)<br>Placebo group receiving saline in TAP block and plain spinal anaesthesia without ITM ($T_S$ vs. $S_S$)<br>TAP block-0.375% bupivacaine 1.0 mg/kg per side | Oral acetaminophen 1 g/6 h + rectal diclofenac 100 mg/18 h + morphine PCA | Pain on movement and morphine consumption was lowest in ITM group was not improved by TAP block<br>Antiemetic use and pruritus was highest in fourth group receiving both ITM and TAP block |
| Eslamian *et al*. (2012) | General anaesthesia | TAP block using landmark technique versus control<br>15 ml of 0.25% bupivacaine per side | Rectal diclofenac 100 mg/24 h + IV tramadol 50 mg/4 h on patient's request | TAP block group had significantly lower VAS score and less tramadol consumption compared to control |
| Tan *et al*. (2012) | General anaesthesia | US-guided TAP block versus control<br>20 ml of 0.25% levobupivacaine per side | Morphine PCA | US-guided TAP block group had significantly lower VAS score and less morphine consumption compared to control |
| Loane *et al*. (2012) | Spinal anaesthesia with 10 µg intrathecal fentanyl<br>100 µg of morphine in ITM groups | US-guided TAP block versus ITM group<br>0.5% ropivacaine 1.5 mg/kg to a maximum of 100 mg per side | Oral acetaminophen 1 g/6 h + oral or rectal naproxen 500 mg/12 h + oral hydromorphone 2-4 mg as needed. If analgesia was still inadequate morphine PCA to be used | TAP block associated with greater morphine requirements and higher pain scores compared to ITM |
| Bollag *et al*. (2012) | Spinal anaesthesia with 10 µg ITF and 100 µg of ITM | US-guided TAP block three groups<br>Placebo group - 20.5 ml of NS in control group<br>BupTAP group - 20 ml of 0.375% bupivacaine + 0.5 ml of NS<br>CloTAP group - 20 ml of 0.375% bupivacaine + 0.5 ml (75 µg) of clonidine | Oral acetaminophen (1 g every 6 h) and diclofenac (75 mg every 8 h) IV morphine as needed and breakthrough pain was treated with oral tramadol (50 mg every 8 h) | No significant difference between three groups in wound hyperalgesia index at 48 h<br>Higher morphine request in placebo group only |

*Contd...*

**Table 2: Contd...**

| Study | Anaesthesia technique | TAP block technique | Post-operative analgesic regime | Outcomes |
|---|---|---|---|---|
| Chandon *et al*. (2014) | Spinal anaesthesia with 5 μg of sufentanil | US-guided TAP block versus CWI<br>TAP block-20 ml of 0.375% levobupivacaine<br>CWI - 250 mg of levobupivacaine in 200 ml of solution at 5 ml/h | Oral paracetamol (1 g), ketoprofen (50 mg) and nefopam (20 mg), four times a day+oral morphine if needed | Study was prematurely terminated after 65 patients due to occurrence of seizure in TAP block group<br>By then 36 patients in TAP block and 29 in continuous completed study; no difference between two groups in pain scores or analgesic requirement |
| Telnes *et al*. (2015) | Spinal anaesthesia (10 mg of 0.5% hyperbaric bupivacaine and 20 μg fentanyl) | Compared US-guided TAP block with wound infiltration<br>TAP block group-20 ml of 0.25% bupivacaine with adrenaline (5 μg/ml)<br>Wound infiltration group-20 ml of 0.25% bupivacaine with adrenaline (5 μg/ml) | Oral paracetamol 1 g 6 hourly, diclofenac 50 mg 8 hourly and IV PCA morphine | No differences in both groups at 48 h cumulative morphine consumption<br>Similar side effects in both groups except for high degree of sedation in TAP block group |
| Singh *et al*. (2013) | Spinal anaesthesia with 10 μg ITF and 100 μg ITM | Compared high dose of ropivacaine 3 mg/kg to a maximum of 300 mg versus low dose 1.5 mg/kg of ropivacaine to a maximum of 150 mg for TAP block | IV ketorolac 30 mg and oral acetaminophen 650 mg were given 6-hourly for the first 24 h + oral codeine 30 mg or oxycodone 5-10 mg every 4 h as rescue analgesics | No difference between groups in post-operative pain scores at 24 h |
| Onishi *et al*. (2015) | Combined spinal epidural | Compared addition of TAP block to epidural morphine<br>Control group received 2 mg of epidural morphine at end of surgery and no TAP group<br>TAP block group- 20 ml of either 0.375% ropivacaine or 0.3% levobupivacaine | PCA morphine | Median time to the first request of morphine was longer and cumulative morphine consumption within 24 h was lower in TAP group |
| McKeen *et al*. (2014) | Spinal anaesthesia with 100 μg ITM and ITF 15 μg | US-guided TAP block<br>TAP block group-20 ml of 0.25% ropivacaine<br>Control group-20 ml of NS | Naprosyn 250 mg 8 hourly + acetaminophen 1000 mg 6 hourly + oxycodone 2.5-5 mg 6 hourly | No clinical difference between the groups in post-operative pain, opioid consumption and side effects |
| Wang *et al*. (2016) | Spinal anaesthesia-10 mg of isobaric bupivacaine with 10 μg of ITF | US-guided TAP block<br>Group TR: 20 ml of 0.375% ropivacaine for TAP block and 50 μg of subcutaneous fentanyl<br>Group TRF: 20 ml of 0.375% ropivacaine with 50 μg of fentanyl in TAP block | 50 mg oral diclofenac + 300 mg of rectal paracetamol + PCA with IV fentanyl | No difference between groups in time to request for the first analgesic, cumulative analgesic consumption and side effects |
| Lee *et al*. (2013) | Combined spinal epidural anaesthesia<br>SAB 9-12 mg of 0.75% hyperbaric bupivacaine + fentanyl 15 μg + morphine 0.25 mg | Compared addition of TAP block to ITM<br>ITM + TAP block compared to ITM + sham TAP block<br>TAP block-20 ml of 0.5% ropivacaine | Mild pain (VRS 1-3)=2 tablets of acetaminophen 500 mg 6 hourly<br>Moderately severe pain (VRS 4-5)=IV ketorolac 30 mg or oral ibuprofen 800 mg every 6 h as needed<br>Severe breakthrough pain (VRS 6-10)=IV morphine 2 mg every 10 min as needed, up to 6 mg or 2 tablets acetaminophen 300 mg/codeine 30 mg or 2 tablets of oxycodone 5 mg/acetaminophen 325 mg 6 hourly | TAP block in conjunction with ITM provided superior analgesia at 2 h post-operative compared to ITM alone<br>No differences by 24 h in two groups in pain scores and analgesic requirements |

TAP – Transversus abdominis plane; SAB – Subarachnoid block; ITM – Intrathecal morphine; SAM – Subarachnoid morphine; PCA – Patient controlled analgesia; IV – Intravenous; VAS – Visual analogue scale; BupTAP – Bupivacaine TAP; CloTAP – Clonidine TAP; CWI – Continuous wound infusion; US – Ultrasound; NS – Normal Saline VRS –Visual Rating Scale

**Table 3: Studies on ilioinguinal-iliohypogastric nerve block for post-caesarean analgesia**

| Study | Anaesthesia technique | II-IH NB technique | Post-operative analgesic regimen | Results | Conclusion |
|---|---|---|---|---|---|
| Sakali *et al*. (2010) | General anaesthesia | 60 parturient are randomly allocated to 2 groups<br>Group I: II-IH NB at the end of surgery using 10 ml of 0.5% ropivacaine on both sides using blind multilevel block<br>Group II: Sham block | PCA tramadol<br>In all patients,<br>rescue analgesia: 0.5 mg/kg of injection meperidine IV if VAS is >3 | Mean VAS scores in II-IH block group were significantly lower than in sham block group at 6th, 8th, 12th, 24th h at rest ($P$<0.05) and at 6th, 8th h with movement ($P$<0.05)<br>Mean total PCA tramadol dose was nearly twice as high in sham block group compared to II-IH block group ($P$<0.05) | II-IH nerve block, performed after CS operations under general anaesthesia, increased the quality of pain control in the post-operative period and apparently decreased the consumption of tramadol |
| Vallejo *et al*. (2012) | Spinal anaesthesia with 0.75% hyperbaric bupivacaine (12 mg) plus morphine (0.15-0.2 mg) and fentanyl (10-20 µg) | Three treatment groups for US-guided II-IH block after CD at the end of surgery<br>Group A: Bilateral 10 mL of 0.5% bupivacaine II-IH block<br>Group B: 10 mL of 0.5% bupivacaine II-IH block on one side and 10 mL of an NSS placebo block on the opposite side (to determine if an effect could be obtained from a one-sided block alone)<br>Group C: 10 mL of bilateral NSS placebo block | IV ketorolac 30 mg 6 hourly<br>In first post-operative day followed by oral analgesics | No difference between groups in terms of pain scores and analgesic consumptions | In parturient receiving ITM for elective CD, II-IH block offers no additional post-operative benefit for up to 48 h |
| Nagshinesh *et al*. (2015) | General anaesthesia | II nerve block at the end of surgery (blind bilateral multiple injection block)<br>80 patients were randomly divided into 2 groups<br>Intervention group: 10 ml of 0.5% bupivacaine on both sides<br>Control group: 10 ml of saline on both sides | Rescue analgesia bolus injections of pethidine if VAS >3 | The mean pain intensity and consumption of pethidine at 6 and 24 h after operation had no significant difference between two groups but in the rest of the times (0, 2, 4 and 12 h), it was different between two groups | II-IH NB reduced the pain intensity and narcotic usage at all-time intervals except at 6 h and 24 h postoperatively |
| Wolfson *et al*. (2012) | Spinal anaesthesia comprising 0.75% hyperbaric bupivacaine (12 mg) plus morphine (0.2 mg) and fentanyl (10 µg) | 34 parturients are randomised into two groups<br>Intervention group: 24 ml of 0.5% bupivacaine at the end of surgery using blind bilateral multiple injection technique<br>Control group: 24 ml saline given bilaterally | Injection ketorolac and oral acetaminophen 500 mg/oxycodone 5 mg | Lower VAS pain scores and longer mean time to first rescue dose of ketorolac was noted in the bupivacaine group (14.3±1.8 h) than the saline group (mean 5.6±1.1 h), ($P$<0.01) | Bilateral multilevel injection II-IH nerve blocks result in lower resting VAS pain scores, lower analgesic requirements and greater satisfaction following CD in patients who received neuraxial morphine |

*Contd...*

**Table 3: Contd...**

| Study | Anaesthesia technique | II-IH NB technique | Post-operative analgesic regimen | Results | Conclusion |
|---|---|---|---|---|---|
| Pekmezci *et al*. (2014) | General anaesthesia | Patients were randomly allocated into one of three groups (*n*=30)<br>Group M: PCA morphine<br>Group MB: PCA morphine + bilateral blind II-IH NB with 15 ml of 0.5% bupivacaine before extubation<br>Group MBP: PCA morphine+bilateral II-IH NB + IV paracetamol 1 g every 6 hourly for 24 h | PCA morphine | Cumulative post-operative morphine consumption for 24 h was significantly higher in Group M than Group MB and group MBP<br>Group M has higher incidences of post-operative pruritus, nausea and vomiting | II-IH NB with or without paracetamol reduces post-operative morphine consumption |

CS – Caesarean section; IV – Intravenous; II-IH NB – Ilioinguinal and iliohypogastric nerve block; NSS – Normal saline; PCA – Patient controlled analgesia; VAS – Visual analogue scale; CWI – Continuous wound infusion; CD – Caesarean delivery; US – Ultrasound

is more efficacious for analgesia as compared to placement above the fascia.[44] However, in the present review, the location of catheter is not the only determinant influencing analgesic efficacy as in only 1 out of 3 trials where the catheter was placed sub fascially reported a positive outcome. The other factors responsible could be the dose of LA used or continuous versus the intermittent boluses of LA through catheter. High concentration–low volume administration of ropivacaine (0.5%, 50 ml) is found to be more effective than low concentration and high volume (0.2%, 125 ml) for direct wound infiltration.[39] Further large-sized studies are required to establish the role of continuous wound infusion with LA in post-caesarean analgesia.

## KETAMINE FOR POST-CAESAREAN PAIN

Ketamine is a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor that inhibits central sensitisation and has a pre-emptive analgesic effect to relieve post-operative pain. In particular, even when ketamine is administered in sub-anaesthetic low doses, it suppresses facilitation of pain related to (NMDA) receptors. A total of eight studies involving evaluation of analgesic efficacy of administration of intravenous ketamine in parturient undergoing CS were identified [Table 5].[45-52] Most of the trials (6 out of 8) used spinal anaesthesia for CS. The timing and the dose of ketamine administered were observed to be variable. In two studies where general anaesthesia was used, ketamine was given before induction of anaesthesia[50,52] whereas in three trials, involving spinal anaesthesia ketamine was administered immediately after subarachnoid block[44,47,48] while in three it was given after delivery of the baby.[46,49,51] Continuous infusion of ketamine was employed in two studies[47,49] and in the remaining trials, bolus doses of ketamine varying from 1 to 0.15 mg/kg were used.

The reported outcomes were variable in these studies; two studies reported a negative outcome,[50,51] two found ketamine to be effective in decreasing consumption of analgesics at 2 h post-operatively[47,52] whereas five studies reported a positive outcome.

These inconsistent results may be related to differences in anaesthesia technique, the dose and technique of ketamine administered and the post-operative analgesic regime used in trials. A recent meta-analysis observed the efficacy of perioperative ketamine in studies where it was administered during regional anaesthesia but not in the studies where the CSs were performed under general anaesthesia.[53] Another important consideration is the plasma volume expansion during pregnancy which can result in insufficient plasma ketamine levels.[54] Therefore, using a higher dose of ketamine or maintaining continuous infusion for longer time might result in adequate plasma levels. However, the psychomimetic side effects of ketamine may preclude this strategy as it impairs the ability of mother to care for newborn in the immediate post-operative period.

## NON-STEROIDAL ANTI-INFLAMMATORY DRUGS AND ACETAMINOPHEN/PARACETAMOL

NSAIDs and acetaminophen are commonly added to a post-caesarean analgesic regimen along with opioid medications to improve post-caesarean pain and reduce opioid requirements. There are two studies investigating role of oral/intravenous acetaminophen either alone or in combination with an NSAIDs

**Table 4: Studies using wound infiltration technique for post-caesarean analgesia**

| Study | Anaesthesia technique | Wound infiltration technique | Post-operative analgesic regime | Outcomes |
|---|---|---|---|---|
| Larsen *et al*. (2015) | SAB (10 mg of hyperbaric bupivacaine and 2.5 μg of sufentanil) | Three groups of patients<br>Ropivacaine 0.5% group: 50 ml of 0.5% ropivacaine (high concentration- low volume group)<br>Ropivacaine 0.2% group: 125 ml of 0.2% ropivacaine (low concentration- high volume group)<br>Placebo group: 50 ml of saline<br>In all three groups, infiltration was done systematically in deep and superficial muscle layers and subcutis | Oral ibuprofen 600 mg + slow release acetaminophen 2 g twice daily + IV sufentanil 0.15 mg/kg if VAS ≥3 + oral ketobemidone 5-10 mg if VAS ≥5 | Rescue analgesics consumption in the ropivacaine 0.5% group was reduced compared with the placebo group ($P$=0.020), and between the ropivacaine 0.2% group and the ropivacaine 0.5% group ($P$=0.044)<br>No difference in pain response among groups |
| Reinikainen *et al*. (2014) | SAB with 0.5% hyperbaric bupivacaine 10-13 mg | Two groups of patients<br>Intervention group: CWI of 0.75% ropivacaine at 2 ml/h for 48 h<br>Control group: 0.9% NSS<br>For wound infusion, a multi-orifice catheter was placed between muscle fascia and subcutaneous tissue | Paracetamol (1 g three times a day) and ibuprofen (600 mg three times a day) for rescue analgesia IM or IV oxycodone | No significant difference in oxycodone consumption between groups<br>No difference in post-operative pain scores, nausea or patient's satisfaction |
| Kainu *et al*. (2012) | Combined spinal epidural anaesthesia<br>SAB-isobaric bupivacaine 10 mg (2.0 mL) + fentanyl 15 μg (0.3 mL) + either saline (0.4 mL) or morphine (160 μg) | Three groups of patients<br>ITM group: 160 μg of morphine+saline; CWI at 5 ml/h<br>Ropivacaine wound infusion group: IT saline 0.4 ml + CWI with 0.375% ropivacaine at 5 ml/h<br>Control group: Saline intrathecally and by the catheter for CWI was placed between parietal peritoneum and transversalis fascia | Oral ketoprofen 100 mg three times a day and IV PCA oxycodone for 24 h | Oxycodone consumption and VAS score was significantly less in ITM group compared to the ropivacaine wound infusion group<br>No significant difference between the ropivacaine wound infusion and saline control groups<br>Pruritus more common in ITM |
| O'Neill *et al*. (2012) | In CWI group - single shot SAB<br>In epidural morphine group-CSE | Two groups of patients<br>CWI: Catheter was placed below fascia after closure of peritoneum<br>Ropivacaine 0.2% at 5 ml/h<br>Epidural morphine group: 2 mg/10 mL bolus of epidural morphine every 12 h (four times) | IV acetaminophen 1 g 6 hourly<br>For breakthrough pain-IM diclofenac 75 mg (up to four times daily) | Median rest pain score at 24 h was significantly lower in CWI group<br>Overall rescue analgesic requirement same in both groups<br>Incidence of nausea or vomiting, pruritus and urinary retention were higher in the epidural morphine group |

*Contd...*

**Table 4: Contd...**

| Study | Anaesthesia technique | Wound infiltration technique | Post-operative analgesic regime | Outcomes |
|---|---|---|---|---|
| Rackleboom *et al*. (2010) | Spinal anaesthesia | Two groups of patients<br>Below fascia group: Multi-orifice catheter was placed between unclosed parietal peritoneum and transversalis fascia<br>Above fascia group-catheter positioned above superficial abdominal fascia<br>Drug for CWI: 5 mL/h for 48 h containing 450 mg ropivacaine and 200 mg ketoprofene in 240 mL isotonic saline | PCA IV morphine | Below the fascia administration of drugs resulted in significant less morphine consumption and less VAS scores |
| Demiraran *et al*. (2013) | General anaesthesia | Three groups<br>Group P: Received 20 mL local wound infiltration with 0.9% saline solution<br>Group L: 20 mL local wound infiltration with levobupivacaine 0.25%<br>Group T: 20 mL local wound infiltration with 1.5 mg/kg tramadol within 0.9% saline solution<br>In all three groups, solution was infiltrated subcutaneously along the skin wound edges | PCA tramadol<br>Rescue analgesics - IV diclofenac 75 mg | Mean 24-h tramadol consumption was lowest in<br>Group T ($P$=0.0001) and it was lower in the Group L compared to Group P ($P$=0.007)<br>No significant difference in pain scores or side effects between the groups |

ITM – Intrathecal morphine; NSS – Normal saline solution; PCA – Patient controlled analgesia; VAS – Visual analogue scale; SAB – Subarachnoid block; CSE – Combined spinal-epidural; IM – Intramuscular; CWI – Continuous wound infusion

as a part of multimodal post-operative analgesic regime.[55,56] Both acetaminophen and diclofenac, when used as a part of post-operative multimodal analgesia, resulted in reduced post-operative analgesic consumption. The combination of diclofenac-tramadol resulted in lower post-operative pain scores compared to diclofenac-acetaminophen.[55] Akhavanakbari *et al*. showed that diclofenac and indomethacin suppositories resulted in less rescue analgesic consumption compared to acetaminophen.[56] These results are consistent with previous studies. There are three studies using COX-2 inhibitors for post-CS analgesia.[57-59] One study evaluated single dose of oral celecoxib 200 mg added to PCEA and compared it to analgesia provided by PCEA only.[57] There was no difference in the total drug consumption in either group. In a study by Wong *et al*., intravenous parecoxib was found to be as effective as ketorolac for post-CS analgesia.[58] It resulted in 22% PCA morphine reduction in the first post-operative day. Paech *et al*. compared the combination of oral celecoxib and intravenous parecoxib to paracetamol for post-CS analgesia.[59] They found that the combination of COX-2 inhibitors to be more effective in reducing analgesic requirement. Celecoxib and parecoxib provide a safe profile for both surgical patients and breastfeeding mothers.

## GABAPENTIN FOR ACUTE AND/OR CHRONIC PAIN FOLLOWING CAESAREAN SECTION

Gabapentin is an anticonvulsant drug with significant analgesic properties. It binds to presynaptic voltage-gated calcium channels in the dorsal root ganglia of the spinal cord and prevents release of excitatory neurotransmitter. It is an established analgesic in chronic and neuropathic pain conditions. The pre-operative use of oral gabapentin has been shown to decrease acute pain after various surgical procedures. There are only two studies in literature exploring the role of gabapentin in post-CS analgesia, and both have conflicting results.[60,61] While one study concluded significant improvement in pain score and maternal

**Table 5: Studies using perioperative low-dose ketamine for post-caesarean analgesia**

| Author | Type of anaesthesia | Intervention | Post-operative analgesic regime | Outcomes |
|---|---|---|---|---|
| Rahmanian *et al*. (2015) | Spinal anaesthesia (12.5 mg of 0.5% hyperbaric bupivacaine) | Study group: 0.25 mg/kg of ketamine as bolus after delivery of baby<br>Control group: Saline as bolus | Rectal diclofenac suppositories and IM pethidine on as needed basis | Study group had significantly longer duration for first rescue analgesic requirement, lower pain score and less total analgesic consumption |
| Han *et al*. (2013) | Spinal anaesthesia (10 mg of 0.5% hyperbaric bupivacaine) | Study group: After spinal anaesthesia 0.5 mg/kg ketamine bolus IV + 0.25 mg/kg/h ketamine infusion during operation<br>IV control group: NSS in same manner IV | PCA fentanyl + IM ketorolac as rescue analgesics | Cumulative dose of fentanyl measured at 2 h after surgery was significantly lower in the ketamine group than; no difference in other time intervals<br>No difference in rescue analgesics and pain score between groups |
| Behdad *et al*. (2013) | Spinal anaesthesia (1.5 ml of 5% lignocaine) | Study group: 30 mg ketamine + 1 mg midazolam IV immediately after spinal anaesthesia<br>Control group: 1 mg midazolam | Meperidine | Mean of post-operative duration until prescribing first analgesic drug in women of ketamine group was significantly longer than women of control group ($P$=0.03)<br>Mean of pain scores in 1st h after CS and consumption of meperidine in ketamine group was significantly lower than control group |
| Suppa *et al*. (2012) | Spinal anaesthesia (0.5% hyperbaric bupivacaine 8-10 mg with sufentanil 5 µg) | Study group: 0.5 mg/kg S-ketamine IM, 10 min after birth, 2 µg/kg/min IV infusion for 12 h<br>Control group: Placebo in the same manner | IV PCA morphine + rescue analgesia with IV ketorolac and oral paracetamol | Morphine consumption was significantly reduced in S-ketamine group at 4-8, 8-12 and 12-24 h<br>S-ketamine group had 31% reduction in total morphine consumption ($P$=0.0005) |
| Bilgen *et al*. (2012) | General anaesthesia | Group I: 0.25 mg/kg IV ketamine<br>Group II: 0.5 mg/kg IV ketamine<br>Group III: 1 mg/kg IV ketamine<br>Group IV: Placebo | IV PCA morphine + rescue analgesia with IM diclofenac | No significant difference between groups in terms of early and late post-operative pain and cumulative morphine consumption |
| Menkitt *et al*. (2012) | Spinal anaesthesia (15 mg of hyperbaric bupivacaine) | IV ketamine 0.15 mg/kg up to 2 ml saline 0.9% immediately after spinal anaesthesia<br>Control: 2 ml saline 0.9% | IM pentazocine and diclofenac on as needed basis | Time of first post-operative analgesia request was significantly longer in ketamine group ($P$<0.001)<br>At 2 h pain scores were significantly lower in ketamine ($P$=0.022)<br>No difference in consumption of analgesics and adverse side effects between two groups |
| Buchat *et al*. (2011) | Spinal anaesthesia (0.75% hyperbaric bupivacaine 12 mg fentanyl 15 and 150 µg morphine) | Study group: IV ketamine 10 mg diluted to 20 ml saline 0.9% after delivery of baby<br>Control: IV 20 ml saline 0.9% | Acetaminophen/ hydrocodone tablets | No difference in incidence of breakthrough pain, pain scores and rescue analgesics<br>Lower pain scores in ketamine group at 2 weeks |
| Reza *et al*. (2010) | General anaesthesia | Study group: Ketamine IV 0.5 mg/kg before induction of anaesthesia<br>Control group: Placebo | IV PCA morphine | Significant lower amount of morphine is used in ketamine group ($P$=0.01) at 2 h postoperatively<br>No significant difference in morphine consumption at 2-24 h<br>No difference in pain scores at different time intervals |

CS – Caesarean section; IV – Intravenous; NSS – Normal saline solution; PCA – Patient controlled analgesia; IM – Intramuscular

satisfaction in first 48 h postoperatively with a single dose of 600 mg, the other study failed to show any beneficial effect of gabapentin. Thus, a definitive conclusion about the use of gabapentin cannot be drawn at this stage, and further studies are warranted to evaluate the effect of gabapentin on acute and/or chronic pain after caesarean section.

## CONCLUSION

From the present review, it is evident that multimodal analgesia including paracetamol, NSAIDs and oral opioids such as oxycodone should be given to all patients unless there are specific contraindications to any of these. Intraoperative interventions which should be considered are first, intrathecal or epidural morphine if regional anaesthesia has been used; and second, TAP block for CS under general anaesthesia. When ITM is included in post-CS analgesic regime, a dose of 50–75 μg balances desirable analgesia with fewer side effects. In future, the possibility of a further lower dose of epidural morphine and role of oral oxycodone as a primary post-operative analgesic regime may be explored. Further studies are needed to define the role of gabapentin, wound infiltration techniques and II-IH NB for post-CS analgesia.

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There are no conflicts of interest.

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